

Clinical Significance of Prognostic Nutritional Index in the Treatment of Esophageal Squamous Cell Carcinoma

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Abstract. *Background/Aim:* The prognostic nutritional index (PNI) is reported to affect postoperative complications and survival of patients with esophageal squamous cell carcinoma (ESCC). The aim of this study is to investigate the clinical significance of PNI in treatment of ESCC. *Patients and Methods:* Two hundred and sixty-three patients who underwent radical esophagectomy were retrospectively analyzed. PNI was calculated in the pretreatment (pre-Tx), post-neoadjuvant chemotherapy (post-NAC), and postoperative periods. *Results:* Pre-Tx PNI positively correlated with prognosis irrespective of undergoing NAC ($p < 0.05$). In the patients with NAC, pre-Tx PNI was one of the independent prognostic factors ($p = 0.04$). In patients with low pre-Tx PNI, the prognosis was improved by increase of PNI after NAC ($p = 0.08$), and two cycles of NAC significantly correlated with high post-NAC PNI ($p = 0.04$). *Conclusion:* Pre-Tx PNI is an independent prognostic factor irrespective of NAC. Patients in whom the post-NAC PNI can be improved have a high probability of obtaining a good prognosis.

Esophageal cancer (EC) is the seventh most common cancer worldwide, and the sixth most common cause of cancer death (1). It is one of the most aggressive malignancies. Early detection and multimodality treatment, which consists of surgery combined with chemotherapy/radiotherapy, may most likely help attain long-term survival (2, 3). In Western

countries, neoadjuvant chemoradiotherapy has been commonly applied for treating resectable advanced EC (4). In Japan, neoadjuvant chemotherapy (NAC) using 5-fluorouracil plus cisplatin (FP) has been recommended as the standard treatment for clinical stage (cStage) II and III esophageal squamous cell carcinoma (ESCC) according to the JCOG9907 study (5). Recently, highly intensive regimens (e.g. combination chemotherapy consisting of docetaxel, cisplatin, and 5-fluorouracil) have been applied in a NAC setting (6, 7).

NAC may have beneficial effects of reducing the tumor bulk and micrometastasis preoperatively but such intensive chemotherapy can also lead to deterioration of the patient's nutritional status due to adverse effects (8, 9). A poor nutritional status is one of the most important problems faced by patients with cancer (10). A poor preoperative nutritional status is associated with postoperative complications, in-hospital mortality, prolonged hospital stay, and poor prognosis in patients with gastrointestinal cancer (11-14).

The prognostic nutritional index (PNI) is calculated using the serum albumin level and total lymphocyte count in the peripheral blood and has been used as a nutritional and immunological indicator (15). Although PNI was originally a predictor of postoperative complications in patients with gastrointestinal cancer (15), it has been recently recognized as an independent predictor of long-term survival for various cancer types, including EC (16-20). However, the significance of PNI as a predictor of NAC effectiveness, or a prognostic factor of patients with EC who underwent NAC has been poorly investigated. In the present study, we evaluated the clinical significance of PNI in patients with ESCC who underwent radical esophagectomy with or without NAC.

Patients and Methods

Patient characteristics and clinical evaluation. We retrospectively reviewed a database containing the clinicopathological and prognostic data of 263 patients who were histologically diagnosed

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Key Words: Prognostic nutritional index, esophageal squamous cell carcinoma, neoadjuvant chemotherapy, esophagectomy, prognosis.

Table I. Background of patients with esophageal squamous cell carcinoma (ESCC).

Characteristic	ESCC (n=263)		p-Value
	No NAC (n=98)	NAC (n=165)	
Age			
Median (range)	67.5 (48-88)	66 (34-83)	0.02
Gender			
Female	11	35	0.03
Male	87	130	
BMI, kg/m ²			
Mean±SD	21.6±3.0	20.7±3.4	0.034
Pre-Tx albumin level (g/dl)			
Mean±SD	4.2±0.4	4.1±0.4	0.08
Pre-Tx lymphocyte count (/μl)			
Mean±SD	1650±628	1862±651	0.01
Pre-Tx PNI			
Mean±SD	50.4±5.3	50.6±4.8	0.75
Post-NAC PNI			
Mean±SD	—	46.9±5.8	—
Postoperative PNI			
Mean±SD	43.6±6.6	43.6±6.7	0.96
Location			
Ce	4	12	0.62
Ut	12	25	
Mt	54	77	
Lt	25	47	
Ae	3	4	
Tumor size, mm			
Mean±SD	41.8±28.1	44.4±29.4	0.49
cT Factor			
T1	71	10	<0.001
T2	7	26	
T3	20	114	
T4	0	15	
cN Factor			
N0	74	42	<0.001
N1	10	47	
N2	10	57	
N3	2	12	
N4	2	7	
cStage			
0	13	0	<0.001
I	53	1	
II	14	55	
III	16	88	
IV	2	21	

ESCC, Esophageal squamous cell carcinoma; NAC, neoadjuvant chemotherapy; BMI, body mass index; Pre-Tx, pretreatment; Post-NAC, post-neoadjuvant chemotherapy; PNI, prognostic nutritional index.

with ESCC between January 2008 and December 2014 and who underwent radical esophagectomy. The median length of the follow-up period for censored cases was 53.6 months (range=1-119 months).

Before initiating the NAC, clinical characteristics were evaluated through upper gastrointestinal endoscopy, computed

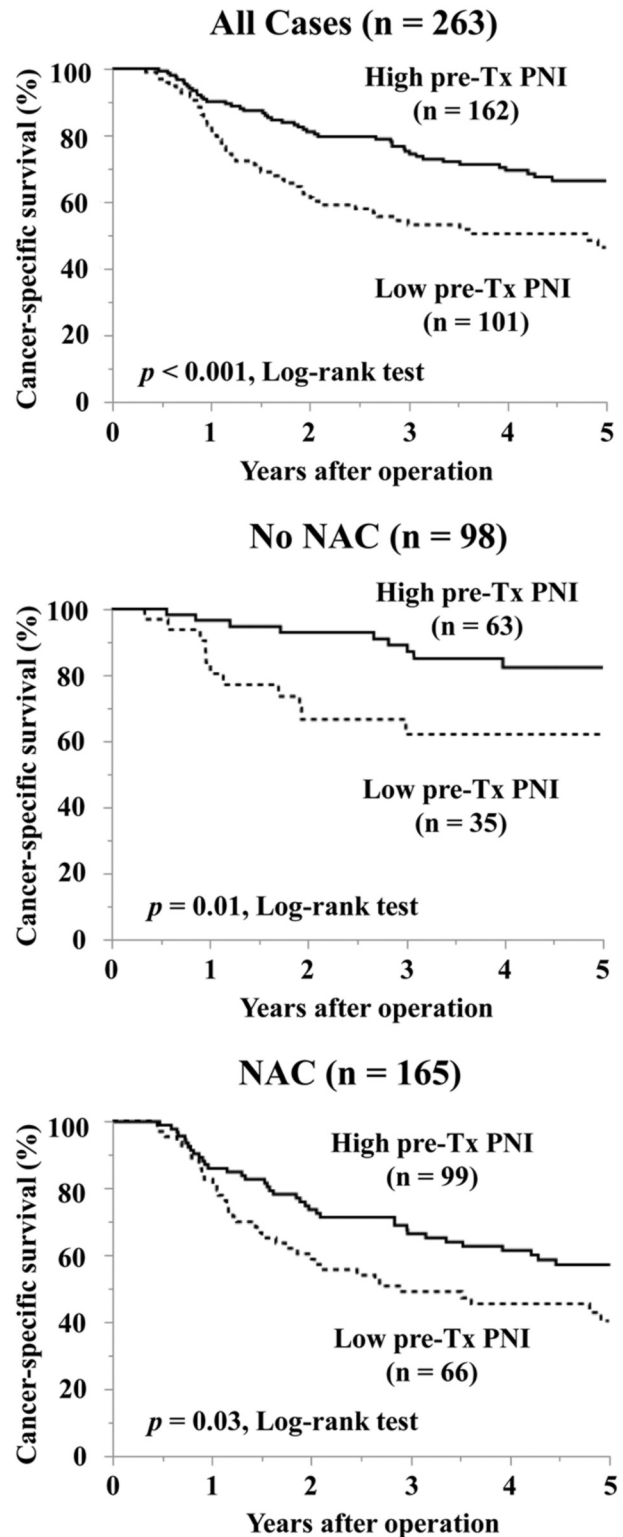


Figure 1. Cancer-specific survival in relation to pretreatment prognostic nutritional index (PNI) status examined using the Kaplan–Meier method in patients treated with and without neoadjuvant chemotherapy (NAC). Patients were divided into groups with high and low pretreatment PNI level using a cut-off value of 49.

Table II. Clinicopathological features in relation to pretreatment prognostic nutritional index (pre-Tx PNI) in patients treated with neoadjuvant chemotherapy (NAC).

Variable	Total patients (n=165)	Pre-Tx PNI		p-Value
		High (n=99)	Low (n=66)	
Age				
≥66 Years	87	51 (52%)	36 (55%)	0.7
<66 Years	78	48 (48%)	30 (45%)	
Gender				
Female	35	21 (21%)	14 (21%)	1
Male	130	78 (79%)	52 (79%)	
Post-NAC PNI				
≥46	94	68 (69%)	26 (39%)	<0.001
<46	71	31 (31%)	40 (61%)	
Postoperative PNI				
≥43	86	54 (55%)	32 (48%)	0.45
<43	79	45 (45%)	34 (52%)	
Tumor size				
≥40 mm	88	53 (54%)	35 (53%)	0.95
<40 mm	77	46 (46%)	31 (47%)	
cT Factor				
T1-2	36	23 (3%)	13 (20%)	0.59
T3-4	129	76 (77%)	53 (80%)	
cN Factor				
N0	42	30 (30%)	12 (18%)	0.08
N1-4	123	69 (70%)	54 (82%)	
cStage				
I-II	56	39 (39%)	17 (26%)	0.07
III-IV	109	60 (61%)	49 (74%)	
Clinical response				
CR/PR	66	33 (33%)	33 (50%)	0.03
SD/PD	99	66 (67%)	33 (50%)	
Histological response				
Grade 0-Ia	109	66 (67%)	43 (65%)	0.84
Grade Ib-III	56	33 (33%)	23 (35%)	
Postoperative complications				
Grade 0-II	128	78 (79%)	50 (76%)	0.65
Grade III-IV	37	21 (21%)	16 (24%)	
Adverse events				
Grade 0-2	93	61 (62%)	32 (48%)	0.1
Grade 3-4	72	38 (38%)	34 (52%)	
Cycles of NAC				
1	21	12 (12%)	9 (14%)	0.78
2	144	87 (88%)	57 (86%)	

Pre-Tx, Pretreatment; PNI, prognostic nutritional index; NAC, neoadjuvant chemotherapy; Post-NAC, post-neoadjuvant chemotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

tomography, and esophagography. The upper gastrointestinal endoscopy and computed tomography were also performed after every cycle of NAC to evaluate the clinical response to chemotherapy. Blood test data were examined before every NAC course and the operation. In order to detect recurrent lesions, the patient was followed-up for at least approximately 5 years postoperatively at an Outpatient Clinic.

Table III. Prognostic factors for patients treated with neoadjuvant chemotherapy (NAC).

Variable	Total patients (n=165)	5-Year CSS (%)	Univariate	Multivariate		
			p-Value	HR	95% CI	p-Value
Pre-Tx PNI						
≥49	99	62.6	0.03	1		
<49	66	45.5		1.64	1.03-2.61	0.04
Post-NAC PNI						
≥46	94	60.6	0.15	–	–	–
<46	71	49.3				
Postoperative PNI						
≥43	86	51.2	0.21	–	–	–
<43	79	60.8				
Tumor size (mm)						
≥40 mm	88	47.7	0.03	1.48	0.91-2.45	0.11
<40 mm	77	64.9		1		
cT factor						
T1-2	36	66.7	0.13	–	–	–
T3-4	129	52.7				
cN factor						
N0	42	66.7	0.1	–	–	–
N1-4	123	52				
cStage						
I-II	56	71.4	0.003	1		
III-IV	109	47.7		1.95	1.13-3.54	0.02
Clinical response						
CR/PR	66	56.1	0.95	–	–	–
SD/PD	99	55.6				
Histological response						
Grade 0-Ia	109	48.6	0.009	2.07	1.21-3.72	0.007
Grade Ib-III	56	69.6		1		
Adverse events						
Grade 0-2	93	60.2	0.19	–	–	–
Grade 3-4	72	50				
Cycles of NAC						
1	21	42.9	0.2	–	–	–
2	144	57.6				

NAC, Neoadjuvant chemotherapy; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; Pre-Tx, pretreatment; PNI, prognostic nutritional index; Post-NAC, post-neoadjuvant chemotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

The clinical and histological responses to NAC were evaluated according to the 11th edition of the Japanese Classification of Esophageal Cancer published in 2017 (21). The severities of postoperative complication were defined according to the Clavien-Dindo classification, version 2.0 (22). Furthermore, adverse events due to chemotherapy were evaluated according to the Common Terminology Criteria for Adverse Events version 5.0 (23).

Determination of PNI and the cut-off value. The serum albumin level and total lymphocyte count were examined in the pre-Tx, post-NAC, and postoperative periods. PNI was calculated as follows: $10 \times \text{serum albumin (g/dl)} + 0.005 \times \text{total lymphocyte count (/mm}^3\text{)}$

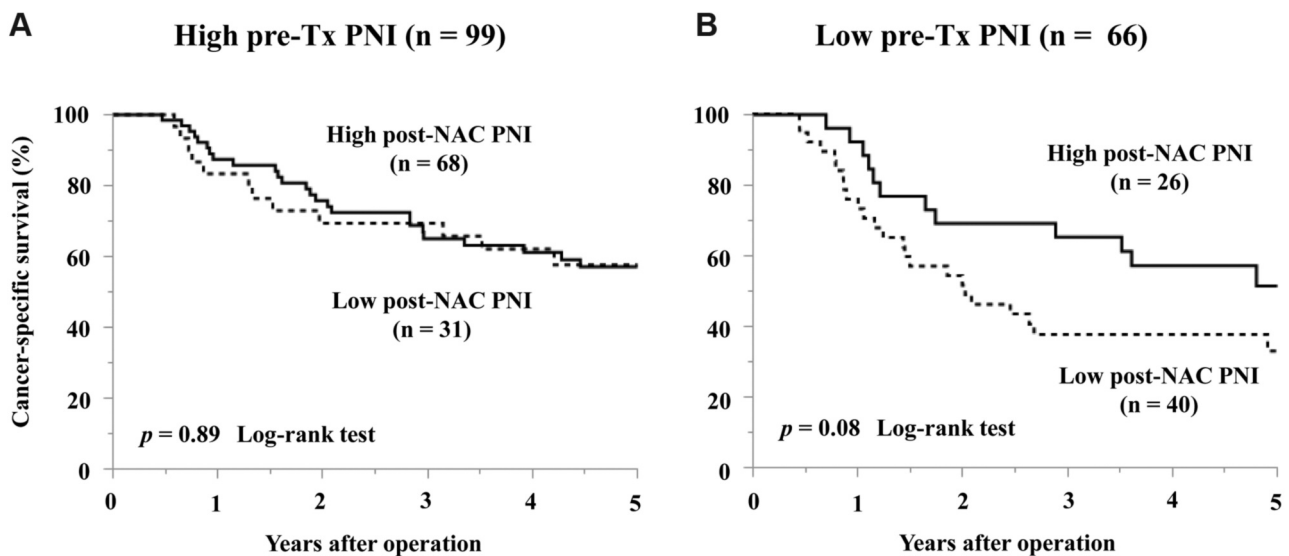


Figure 2. Cancer-specific survival of patients with high (A) and low (B) pretreatment (pTx) prognostic nutritional index (PNI) treated with neoadjuvant chemotherapy (NAC) is shown according to the post-NAC PNI, using a cut-off value of 46.

(15). The cut-off values of PNI in each period were determined as 49, 46, and 43, respectively, by analysis of the receiver operating characteristics curve using the PNI value and prognostic data. Patients were divided into two groups, namely high PNI and low PNI, using these cut-off values.

Treatment courses. Most of the NAC procedures were performed with the FP regimen according to JCOG 9907 (5). In the FP regimen, 80 mg/m² of cisplatin was administered on day 1, and 800 mg/m² of 5-fluorouracil was administered from day 1 to day 5 (24). Two courses of this regimen were conducted every 3 weeks. The docetaxel, cisplatin, and 5-fluorouracil regimen was provided for some patients who were clinically diagnosed with lymph node metastasis. A total of 144 patients completed the two courses of neoadjuvant FP therapy, and 21 other patients underwent only one course of NAC due to adverse events or inadequate tumor control. All patients underwent radical esophagectomy with two or three fields of lymph node dissection; 56 patients underwent three-field lymph node dissection (21.3%). The reconstruction was generally performed using gastric tube *via* retrosternal route. Ileocolic or posterior mediastinal route reconstruction was sometimes performed in accordance with the patient's condition.

Statistical analysis. Categorical variables are presented as numbers and percentages, and the groups were compared using the chi-square test or Fisher's exact test. Continuous variables are shown as the average and range, and the averages were compared using the *t*-test. Cancer-specific survival was measured from surgery for EC. Survival curves were estimated using the Kaplan-Meier method, and the differences were calculated using the log-rank test. Multivariate analysis was performed using the Cox proportional hazard model. Furthermore, all statistical analyses were performed using the statistical software JMP (version 13 for Windows, SAS Institute, Cary, NC, USA), and a value of *p* < 0.05 was considered statistically significant.

Results

Patient background and PNI value. The clinicopathological features of all patients are summarized in Table I. Among the 263 patients, 165 received NAC, and this was significantly associated with advanced disease. The pre-Tx albumin level and lymphocyte count were significantly different between patients treated with and without NAC (*p* = 0.01 and *p* = 0.004, respectively). However, the mean pre-Tx PNI values of 50.6 and 50.4 in patients with and without NAC were not significantly different between two groups (*p* = 0.73). Similarly, the postoperative PNI values were not different (*p* = 0.95).

Survival analysis in relation to pre-Tx PNI. Figure 1 indicates the results of the survival analysis in relation to pre-Tx PNI. The prognosis of patients with low pre-Tx PNI was significantly worse than that of those with high pre-Tx PNI considering the whole patient cohort (*p* < 0.001). Moreover, this pattern was similar for patients treated with and without NAC (*p* = 0.01 and *p* = 0.03, respectively).

Relationship between the pre-Tx PNI value and clinicopathological features in patients treated with NAC. Table II presents the clinicopathological features in relation to the pre-Tx PNI level in patients treated with NAC. Post-NAC PNI and clinical response were significantly positively associated with the pre-Tx PNI level (*p* < 0.001 and *p* = 0.03, respectively). Clinical N factor (*p* = 0.08), cStage (*p* = 0.07), and adverse events (*p* = 0.10) were not significantly related to the pre-Tx PNI level. In addition, the pre-Tx PNI did not

correlate with the occurrence of postoperative complications and the effects or adverse events of NAC.

Prognostic factors of patients treated with NAC. In the univariate analysis, the pre-Tx PNI ($p=0.03$), tumor size ($p=0.03$), cStage ($p=0.003$), and histological response ($p=0.009$) were found to be prognostic factors (Table III). In the multivariate analysis, the pre-Tx PNI (HR=1.64, 95% CI=1.03-2.61; $p=0.04$), cStage (HR=1.95, 95% CI=1.13-3.54; $p=0.02$), and histological response (HR=2.07, 95% CI=1.21-3.72; $p=0.007$) were independent prognostic factors in patients with NAC.

Subgroup analysis of survival according to post-NAC PNI level. In patients with high pre-Tx PNI, no significant difference was observed in survival between the groups with high and low post-NAC PNI ($p=0.89$, Figure 2A). However, in patients with low pre-Tx PNI, high post-NAC PNI was related to a better prognosis than low post-NAC PNI ($p=0.08$, Figure 2B). Furthermore, high post-NAC PNI was significantly associated with the completion of two planned cycles of NAC ($p=0.04$, Table IV).

Discussion

The prognostic value of PNI in patients with EC has been extensively investigated (11, 16). For instance, Feng and Chen demonstrated that the preoperative PNI is an independent predictor of cancer-specific survival in patients with EC (16). In another study, PNI correlated with the depth of tumor invasion, lymph node metastasis, and tumor stage in patients with gastric and colorectal cancer (17, 19). However, as far as we are aware, no article exists that examined the relationship between prognosis and PNI in each treatment course, including NAC. Herein, we found that the prognosis of patients with high pre-Tx PNI was significantly better irrespective of whether they underwent NAC, and the pre-Tx PNI was an independent prognostic factor in patients treated with NAC. Thus, preoperative nutritional status and immunity may be associated with the therapeutic effectiveness of NAC or the prognosis of advanced cancer. Low nutritional status and immunity to cancer cells may promote the proliferation of blood-circulating tumor cells (18), and PNI reflects the extent of tumor progression (16, 19, 25). However, in the present study, the relationship between pre-Tx PNI and the therapeutic effectiveness of NAC was not confirmed.

Chemotherapy can paradoxically cause both deterioration and improvement of the nutritional status due to toxicities and overall tumor reduction (26). Nutritional parameters, such as the body mass index, serum albumin, and hemoglobin following chemotherapy or chemoradiotherapy are significantly reduced in patients with EC (24, 27). Therefore, the differences of nutritional status immediately before

Table IV. *Clinicopathological features in relation to prognostic nutritional index (PNI) post neoadjuvant chemotherapy (NAC) in patients with low pre-Tx PNI.*

Variable	Total patients (n=66)	Post-NAC PNI		p-Value
		High (n=26)	Low (n=40)	
Age				
≥66 Years	36	12 (46%)	24 (60%)	0.27
<66 Years	30	14 (54%)	16 (40%)	
Gender				
Female	14	5 (19%)	9 (23%)	0.75
Male	52	21 (81%)	31 (77%)	
Postoperative PNI				
≥43	32	14 (54%)	18 (45%)	0.48
<43	34	12 (46%)	22 (55%)	
Tumor size (mm)				
≤31	35	14 (54%)	21 (53%)	0.91
>31	31	12 (46%)	19 (47%)	
cT Factor				
T1-2	13	6 (23%)	7 (18%)	0.58
T3-4	53	20 (77%)	33 (82%)	
cN Factor				
N0	12	7 (27%)	5 (13%)	0.14
N1-4	54	19 (73%)	35 (87%)	
cStage				
I-II	17	9 (35%)	8 (20%)	0.19
III-IV	49	17 (65%)	32 (80%)	
Clinical response				
CR/PR	33	14 (54%)	19 (48%)	0.61
PD/SD	33	12 (46%)	21 (52%)	
Histological response				
Grade 0-Ia	43	15 (58%)	28 (70%)	0.31
Grade Ib-III	23	11 (42%)	12 (30%)	
Postoperative complications				
Grade 0-II	50	22 (85%)	28 (72%)	0.17
Grade III-V	16	4 (15%)	12 (28%)	
Adverse events				
Grade 0-2	32	15 (58%)	17 (43%)	0.23
Grade 3-4	34	11 (42%)	23 (57%)	
Cycles of NAC				
1	9	1 (4%)	8 (20%)	0.04
2	57	25 (96%)	32 (80%)	

PNI, Prognostic nutritional index; NAC, neoadjuvant chemotherapy; Pre-Tx, pretreatment; Post-NAC, post-neoadjuvant chemotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

undergoing NAC and surgery may accurately predict the long-term survival of patients receiving NAC.

Patients with EC are often malnourished and difficult to optimize nutritionally. While evidence suggests that neoadjuvant therapy can offer a survival advantage, associated toxicity can exacerbate an already poor nutritional status. There is currently no accepted standard of care regarding the optimal nutritional approach. However, the effects of nutritional intervention for patients with EC have been evaluated (28-30). Fietkau *et al.* found that immunonutrition

consisting of n-3 polyunsaturated fatty acids improved the nutritional score in patients with head and neck cancer treated with chemoradiotherapy (28). Cools-Lartigue *et al.* reported that dietary counseling under the supervision of a specialized nutritionist can effectively maintain the body mass index and serum albumin levels during NAC in patients with esophageal adenocarcinoma (29). In the systematic review of Huddy *et al.*, the optimal nutritional approach during NAC prior to the surgical resection of EC was unclear because of the limitation in case series, there being few prospective multicenter or comparative studies (30). In the present study, in the group with low pre-Tx PNI, the prognosis of patients with high post-NAC PNI was improved compared with those with low post-NAC PNI. The effects of nutritional intervention employed during NAC on long-term outcomes remain unexplored.

The present study has some limitations. This study is a retrospective observational study involving a small number of cases. Therefore, in order to improve the nutritional status and prognosis of patients with ESCC, prospective interventional trials are needed to clarify the optimal nutritional intervention during NAC. In addition, the evaluation of nutritional status may most likely have created some biases because of obstruction due to tumor-induced stenosis and the volume of consumed fluids, including any nutrients or parental nutrition, were not examined. These factors will affect the improvement of the nutritional status.

In conclusion, pre-Tx PNI is considered a prognostic factor irrespective of undergoing NAC. Patients in whom can PNI can be maintained or improved during NAC have a high probability of completing chemotherapy and obtaining a good prognosis. A nutritional intervention may be effective for patients with EC to maintain their nutritional status and improve prognosis.

Conflicts of Interest

The Authors have no conflicts of interest that should be disclosed in this research.

Authors' Contributions

Takao K, Konishi H, Fujiwara H and Shiozaki A designed the research; Shoda K, Kosuga T, Kubota T, Arita T, Morimura R, Murayama Y, Kuriu Y, Ikoma H, Nakanishi M and Okamoto K performed the research; Takao K and Konishi H performed the research and analyzed the data; Takao K, Konishi H, Fujiwara H and Otsuji E critically revised the manuscript for important intellectual content.

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Received May 8, 2020

Revised July 15, 2020

Accepted July 16, 2020